

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

METHOD AND DEVICE FOR
CONTROLLING LIQUID FLOW
ON THE SURFACE OF A MICROFLUIDIC CHIP

5

Background of the Invention

This application claims priority of U.S. Provisional Application Serial No. 60/245,119 filed November 2, 2000, U.S. Provisional Application Serial No. 60/248,860 filed November 9, 2000 and U.S. Provisional Application Serial No. 60/248,861 filed 10 November 9, 2000 which are hereby incorporated by reference.

1. Field of the Invention

The present invention relates to control of liquid flows on a microfluidic chip and in particular to routing, reacting and mixing liquid microstructures on the surface of a 15 rigid or flexible substrate using a combination of one or more of the following: high resolution temperature control at individual addressable electronic elements for generating thermocapillary flow of the liquid; surface patterning for confining the liquid at one or more particular locations on the chip; obtaining heterogeneous surfaces with hydrophilic and hydrophobic regions; and retaining hydrophilicity of surfaces.

20 2. Description of the Related Art

Technological developments in the miniaturization and integration of multiple functionalities for chemical analysis and synthesis into a hand held device have generated interest in developing efficient methods for transporting ultra small volumes of liquid through networked arrays. Conventional techniques include micromechanical and 25 electric field driven methods for manipulating and controlling flow including pneumatic actuation, electro-osmotic, electrophoretic or electrowetting techniques, centrifugation and magnetic field driven pumping.

U.S. Patent No. 6,124,138 describes a device for detecting or quantitating one or more of a plurality of different analytes in a liquid sample. The device includes a sample distribution network having a sample inlet, one or more detection chambers and a dead 30 end fluid connection between the chambers and the inlet. A liquid sample is applied to the sample inlet and is drawn by vacuum action to deliver the sample to the detection

chambers. The delivered sample reacts with at least one analyte specific reagent in each detection chamber under conditions effective to produce a detectable signal. A temperature controller can be used to heat or cool the detection chambers to facilitate reaction of the sample with the analyte detection reagents.

5 U.S. Patent No. 6,306,273 describes a method for transporting a liquid in a channel of a microfluidic system by electrokinetic action in which a liquid containing material comprises a plurality of charged chemical species. A voltage is applied from one point along the channel to a different point along the channel whereby the charged chemical species are transported along the channel. Fields in the range of 200-600 V/cm
10 are typically used to control the electro-osmotic flow.

One developed thermally based device uses thermocapillary pumping for pushing discrete liquid droplets through an enclosed microfabricated channel, as described in T.S. Sammarco and M.A. Burns, Thermocapillary Pumping of Discrete Drops in Microfabricated analysis devices [AIChE Journal 45:350-366 (1999)]. This device allows 15 discrete liquid plugs to advance through an interior channel by locally heating or cooling one of the droplet endcaps which induces a differential in capillary pressure. Micromechanical devices have the limitation that moving parts, such as miniature pumps and gears, often suffer leakage and degradation under wear. Electrokinetic and 20 pneumatic techniques have the limitation that because the flow is confined to interior channels, particulates and aggregates in solution can block flow and destroy pumping action. Electrically based methods typically require external supply voltages of several kV. Each of the above-described devices also has the limitation of being capable of handling either continuous streams or discrete droplets but not both due to the flow mechanism on which they are based.

25 The mixing of liquids in microscale devices is often difficult to attain due to the absence of turbulent phenomena. Many devices therefore rely on the action of diffusion and laminar flow. It is therefore desirable to provide a method and system for routing, reacting and mixing small volumes of liquid on the surface of a substrate, without the need for moving parts, high pressure or vacuum. It would also be advantageous to operate 30 such devices using low voltages which are compatible with conventional integrated circuits.

Summary of the Invention

The invention is directed to a method and device for routing, mixing, or reacting droplets or liquid microstreams along the surface of a flat substrate. The flow of liquid microstreams or microdroplets along designated pathways is confined by chemical surface patterning. Individually addressable heating elements, which are embedded in the substrate, can be used to generate flow via thermocapillary effects or to trigger or quench chemical reactions. The open architecture allows the liquid to remain in constant contact with the ambient atmosphere. The device can be used for microfluidic applications or as a surface reactor or biosensor, among other applications.

Thermocapillary actuation is based on the surface stress created by variations in surface tension at a gas-liquid or liquid-liquid interface. Variations in surface tension are created by temperature differences along such interfaces which can be directly applied by contacting the liquid to a differentially heated surface. For sufficiently thin liquid films in which the overlying fluid is a gas, the thermal map applied to the substrate is reproduced at the gas-liquid interface.

In an embodiment of the present invention, a liquid is received on a patterned surface comprising one or more pathways. The patterned surface can be formed of one or more hydrophobic regions confining a hydrophilic surface in which the liquid flows along the hydrophilic surface. One or more of a plurality of heating elements are in registry with the patterned surface. The heating elements are individually activated under conditions effective for routing the fluid on the patterned surface. The activated heating elements form a thermal map. In an embodiment of the present invention, activation of the thermal map divides a liquid stream into one or more droplets. In another embodiment, activation of the thermal map initiates or quenches a reaction. In another embodiment, activation of the thermal map effects mixing of two or more streams or two or more droplets. Alternatively, activation of the thermal map traps or releases one or more droplets.

In one aspect of the present invention, an airborne material is absorbed in liquid received on the device. The airborne material is detected in the liquid. In a further aspect, a method is described for fabrication of the device. In another aspect, a method is described for forming refreshable hydrophobic and hydrophilic surfaces. The refreshable

surfaces can be used with the device of the present invention. In another aspect a method is provided for storing the device.

The invention will be more fully described by reference to the detailed description when read in light of the following drawings.

5

Brief Description of the Drawings

Fig. 1 is a cross section of one embodiment of the thermal fluidic device in accordance with the teachings of the present invention.

10 Fig. 2 is a schematic diagram of an embodiment of an arrangement of heating elements in an active-matrix array including an electronic addressing scheme.

Fig. 3 is a schematic diagram of one embodiment of a heater cell in an active-matrix array.

15 Fig. 4a is a diagram of an electronically controlled thermal map for providing flow of a continuous stream of fluid by application of a linearly decreasing temperature profile.

Fig. 4b is a diagram of an electronically controlled thermal map for dividing a continuous stream of liquid into droplets by application of a zig-zag shaped temperature profile.

20 Fig. 4c is a diagram of an electronically controlled thermal map for droplet isolation and trapping and subsequent heating or cooling.

Fig. 4d is a diagram of an electronically controlled thermal map for moving a previously trapped droplet.

Fig. 5 is a plan view of a possible network of hydrophilic surface pathways.

25 Fig. 6a is a schematic diagram of an initial conformation of two liquids to be mixed which are supported on a differentially heated substrate.

Fig. 6b is a schematic diagram of thermocapillary driven mixing of two fluids enforced by an electronically controlled differentially heated substrate.

Fig. 7a is a schematic diagram of a square shaped hydrophilic reservoir.

Fig. 7b is a schematic diagram of a circular shaped hydrophilic reservoir.

30 Fig. 7c is a schematic diagram of a diamond shaped hydrophilic reservoir.

Fig. 8a is a schematic diagram of a network comprising a linear pathway connecting a source and target reservoir.

Fig. 8b is a schematic diagram of a network of a plurality of linear pathways connecting a source and target reservoir.

5 Fig. 8c is a schematic diagram of a sinuous pathway connecting a source and target reservoir.

Fig. 9a is a schematic diagram of a network including a plurality of vertical pathways having a plurality of reservoirs interconnected to a horizontal pathway.

10 Fig. 9b is a schematic diagram of a network comprising rectilinear intersecting pathways.

Fig. 9c is a schematic diagram of a network comprising a radial arrangement of pathways.

Fig. 9d is a schematic diagram of a network including a plurality of vertical pathways intersecting a horizontal pathway.

15 Fig. 9e is a schematic diagram of a plurality of horizontal pathways connected by an intersecting sinuous pathway.

Fig. 10 is a schematic diagram of various dispensing geometries for introducing fluid onto hydrophilic pathways.

20 Fig. 11a is a plan view of one embodiment of the thermal fluidic device as a gas sensor or biosensor.

Fig. 11b is a bottom view of one embodiment of the thermal fluidic device as a gas sensor or biosensor.

Fig. 12 is a flow diagram of an exemplary process for fabrication of the device.

25 Fig. 13 is a flow diagram of a method for forming a refreshable hydrophobic surface pattern.

Detailed Description

The following terms and phrases as used herein are intended to have the meanings below. The term "surface pathways" refers to either a flat topology with chemical patterning or an indentation, ridge or groove optionally having chemical patterning. The 30 term "hydrophilic pathways" refers to hydrophilic lanes surrounded by hydrophobic

regions such that an appropriate liquid sample will remain confined to the hydrophilic portions. The hydrophilic pathways can be flush with the hydrophobic layer or include ridges or grooves.

The term "hydrophilic" refers to a surface which is either completely or partially wetted by the liquid sample, in contrast to a hydrophobic surface on which the liquid assumes a contact angle exceeding ninety degrees. The contact angle is defined at the interior tangent angle of the air-liquid interface at the three phase boundary consisting of the gas, liquid and solid phases.

Reference will now be made in greater detail to embodiments of the invention, examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference numerals will be used throughout the drawings and the description to refer to the same or like parts.

Fig. 1 illustrates a cross-sectional view of an exemplary device 10 in accordance with the teachings of the present invention. Device 10 includes substrate 12. Substrate 12 can be formed of any solid material whether rigid or flexible which is suitable for use in combination with components described below. Exemplary suitable materials for substrate 12 include various plastic polymers and copolymers, such as polypropylene, polystyrenes, polyimides and polycarbonates. Substrate 12 can also be formed of inorganic materials such as glass, metal or silicon. Substrate 12 can be formed from a single material or from a plurality of materials.

Surface 11 of substrate 12 is coupled to heat sink 13. Heat sink 13 can be formed of any heat transfer device capable of removing heat from device 10. For example, heat sink 13 can be a Peltier cooler device or a metal block cooled by a steady internal flow of coolant.

Passivation layer 9 can be optionally coupled to surface 15 of substrate 12 to provide a reproducible surface for subsequent processing steps or to improve the mechanical adhesion of subsequently deposited layers.

Insulator layer 14 can be optionally coupled to surface 15 of substrate 12 or passivation layer 9. Insulator layer 14 can be formed of a material suitable for providing thermal and/or electrical insulation. Alternatively, if substrate 12 is formed of a material with low thermal conductivity, insulator layer 14 is not required. Examples of suitable

materials for insulator layer 14 include polyimides or other polymeric or organic materials, as well as organic or inorganic porous materials.

A plurality of heating elements 16 are deposited onto insulator layer 14 or directly onto substrate 12, if insulator layer 14 is not used. Planarization and electrical insulation 5 layer 8 is deposited over heating elements 16 and exposed surfaces of insulation layer 14 or substrate 12. Heating elements 16 are embedded in insulation layer 8. Patterned surface layer 18 is in registry with heater elements 16. Patterned surface layer 18 can include hydrophobic portions patterned on a hydrophilic layer. Optionally planarization aspect of layer 8 can be deposited on top of heater elements 16 if a flat surface topology 10 is desired for subsequent processing or device operation. For cases in which the liquid being transported is volatile, the device can be encapsulated with an overlying glass or plastic containing surface 17 whose interior region may be saturated to reduce evaporation.

Liquid microstructures contact the hydrophilic regions of patterned surface layer 15 19 as described in more detail below. Suitable liquids include, but are not limited to water, glycerol, tetra(ethylene glycol), polydimethylsiloxane, organic solvents, cell cultures, animal or human bodily fluids, solutions comprising suspended particles, solutions comprising biological molecules, cellular cytoplasm, cellular extracts, cellular suspensions, solutions of labeled particles or biological molecules, solutions comprising 20 liposomes, encapsulated material, or micelles, etc. In another embodiment of the invention, the liquid can further contain solid particulates or other droplets, as in a liquid emulsion. By way of example, but not by way of limitation, particulates are any polymer particle, such as polystyrene particles or beads, metal colloids (e.g., gold colloidal particles), magnetic particles, dielectric particles, nanocrystals of materials, and 25 bioparticles, such as spores, pollen, cellular occlusions, precipitates, intracellular crystals, etc. In possible embodiments of the invention, the particles are in the nanometer and/or micrometer size range, for example, but not limited to, from about 1 nm to about 100 μm .

In still another embodiment of the invention, the liquid contains biological molecules, such as but not limited to, polynucleotides such as DNA and RNA, 30 polysaccharides, polypeptides, proteins, lipids, and any other cellular components.

In an embodiment of the invention, the liquid comprises viruses, such as but not limited to, viruses capable of infecting any organisms including microorganisms, plants or animals, in particular, mammals and especially humans. Further, viruses in the categories of viruses with or without coat and viruses categorized as DNA or RNA 5 viruses, either double stranded or single stranded are encompassed by the present invention.

In yet another embodiment, liquid further comprises one or more biological cells which are capable of being routed, mixed or reacted with species present on device 10. The biological cells are either procaryotic and/or eucaryotic cells. Examples of 10 procaryotic cells include, but are not limited to, bacteria, microorganisms, etc. Examples of eucaryotic cells are, but not limited to, fungal, plant and animal cells for instance mammalian cells or human cells. In more particular embodiments, the mammalian or human cells may be cells for example, from blood, liver, kidney, lung or any other tissue or organ. In another preferred embodiment, the cells are tumor or cancer cells, which can 15 be either benign or malignant cancer cells.

In a typical embodiment of the thermal fluidic device, the width of the patterned hydrophilic pathways will range from a few micrometers to hundreds of micrometers. Liquid samples deposited onto the reservoirs or hydrophilic pathways can range from less than a microliter to tens of microliters. The liquids flowing along the hydrophilic 20 pathways can range in thickness from about a micron to tens or hundreds of microns, depending on the degree of hydrophobicity of the surrounding material. The more hydrophobic is the surrounding surface to the hydrophilic liquid, the thicker the liquid stream or droplet that can be confined by the chemical patterning. A range of thermal gradients can be applied to the chemically patterned surface so long as the liquid does not 25 substantially evaporate or boil. Typical thermal gradients can range from a few degrees per centimeter to tens of degrees per centimeter. The speed of the flowing liquid depends on material properties like the liquid surface tension, the variation of surface tension with temperature and the liquid viscosity. The speed also depends on the magnitude of the applied thermal variation with distance (i.e. the local or global thermal gradient), as well 30 as geometric features of the device like the surface area of the reservoir (which controls the volume of sample deposited), the width, length and shape of the hydrophilic pathway

connecting source to target. Studies with liquids like tetraethylene glycol can produce speeds in the range of 600 micrometers per second. Designs with geometric and chemical patterning techniques that allow thicker films to flow onto a hydrophilic pathway can produce speeds of the order of a millimeter per second.

5 Fig. 2 illustrates an arrangement of heating elements 16 in array 19. Array 19 comprises a plurality of cells 20 arranged in a matrix configuration. As shown in Fig. 3, each individual cell 20 can be an integrated circuit comprising one or more transistors 21, capacitors 21b and microheating elements 16. Each heating element 16 sets the temperature of a respective cell 20. Each cell 20 is addressed by thin film transistor switch 21a. Transistor 21a switches power to capacitor 21b and transistor 23. Voltage on transistor 23 sets current through capacitor 23 thereby regulating its temperature heating element 16. In this embodiment, the matrix configuration is a 3-by-3 matrix. It will be appreciated that alternate size matrices can be used depending on the size of device 10 or the desired configuration of a thermal map associated with the matrix configuration. Heating elements 16 are selected to have a predetermined size dependent on the desired size of device 10 and the desired positional resolution of the temperature profile. For example, heating elements 16 typically can have a width in the range of about 1 micron to about 5 mm. VDD is a power supply voltage to cell 20.

10 Liquid streams or droplets can be moved from one cell 20 to another cell 20 with a speed determined by the applied thermal map, the liquid viscosity, the surface tension and the variation in surface tension with temperature. Cells 20 can be activated at a rate faster than the rate of fluid motion in order to establish the temperature of each cell 20 ahead of the fluid response. Liquid 24 responds by flowing from cells at higher temperature to cells at lower temperature.

15

20

25 Alternative thermal maps can be applied to effect conformational changes to a liquid stream controlled by device 10 as shown schematically in Figs. 4a-d. The vertical axis is the temperature at a particular location (x,y) on the surface of device 10. Fig. 4a describes the type of thermal map which will provide continuous streaming of a liquid rivulet or droplet across a series of cells 20. Fig. 4b describes the action of a saw-tooth temperature profile which will divide a liquid rivulet into a series of discrete droplets. These droplets may be monodisperse or not depending on the particular thermal pattern

5 applied and the lateral extent of the heating elements. Fig. 4c describes a thermal map for isolating and trapping a discrete droplet and subsequent heating and cooling to initiate or quench a chemical reaction. After the droplet has been appropriately manipulated, the thermal map shown in Fig. 4d can be applied for release and further migration onto another cell 20, a reservoir or exit port from the device.

In one embodiment of the present invention, surface layer 18 is patterned with network 29 of intersecting pathways, as shown in Fig. 5. Surface layer 18 can be formed of a hydrophilic material for forming hydrophilic pathways between hydrophobic regions.

10 Horizontal pathways 30a-30c extend respectively between reservoirs 31a-31c and reservoirs 32a-32c. Vertical pathways 33a-33c extend respectively between reservoirs 34a-34c and reservoirs 35a-35c. Each of horizontal pathways 30a-30c intersects vertical pathways 33a-33c. A matrix of cells can be in registry with horizontal pathways 30a-30c and vertical pathways 33a-33c for controlling flow from respective reservoirs (not shown). First reagent 36a is dispensed into reservoir 34b and second reagent 36b is dispensed from reservoir 34c. First reagent 36a can be the same or different than second reagent 36b. Third reagent 36c is dispensed from reservoir 30a. Each of first reagent 36a, second reagent 36b and third reagent 36c flows toward fluid reservoir 35c. First reagent 36a and third reagent 36c flow in pathway 30a and are mixed with one another to form a homogeneous composition. Second reagent 36b flows into pathway 33c and is mixed with the mixture of first reagent and third reagent 36c flowing in pathway 33c toward reservoir 35c to form a homogeneous composition. A chemical reaction between two or more of reagents 36a – 36c or an entity such as a molecule, particle or droplet immobilized in one of channels 30a, 33c or reservoir 35c can occur spontaneously or can 15 be induced by activation of one or more heating elements in registry with pathways 30-30c and 33a-33c. It will be appreciated that various reagents can be dispensed from one or all of the pathways in network 29.

20

25 Liquid mixing can be achieved by placing liquid in contact with a differentially heated substrate. Fig. 6a is a cross sectional view illustrating the mixing of two liquids, 30 and 42, residing on a hydrophilic region. Liquids 40 and 42 represent cross-sectional views of a discrete droplet or a liquid rivulet. In the absence of a lateral thermal gradient

on substrate 44, liquid 40 and 42 can only mix by interdiffusion. In the presence of a lateral thermal gradient on substrate 44, liquids 41 and 42 mix by thermocapillary induced forcing to produce the mixing pattern shown in Fig. 6b. For the case of a liquid made to flow by application of an additional thermal gradient perpendicular to the first, 5 the spiral pattern shown will evolve into a helical one. The creation of additional interfacial area between liquids 40 and 42 produces significantly faster mixing.

Reservoirs containing liquids to be dispensed can be patterned into a variety of shapes as illustrated in Figs. 7a-7c. Exemplary shapes include a square, circle or diamond. These can also be combined to produce rectangles, polygonal or curvilinear shapes.

10 Alternative geometric layouts for surface pathways connecting two reservoirs are illustrated in Figs. 8a –8c. Network 50 represents a linear pathway 52 connecting reservoir 51 to 53. Network 54 includes three linear pathways 52a-52c connecting reservoir 51 to 53, as shown in Fig. 8b. Network 55 consists of a sinuous pathway 56 connecting reservoir 51 to 53, as shown in Fig. 8c. Networks can comprise a source and a 15 target reservoir connected by one or more pathways. The pathways can be rectilinear or curvilinear. The subsurface heater elements 16 are placed in registry with the network to achieve the desired flow pattern. The minimum number of heater elements required for controlling the flow of liquid into or out of a reservoir connected to N pathways equals N+1. One heater element is used for uniformly heating or cooling the reservoir pad while 20 the remaining N heater elements function as valves to prevent or promote migration along the N pathways. The number of heater elements 16 used for controlling the flow of liquid along a pathway depends on the length L of the pathway and the desired spatial resolution D.

Figs. 9a-9e represent schematic diagrams of possible network variants connecting 25 sets of reservoirs. Fig. 9a illustrates a network including a plurality of vertical pathways having a plurality of reservoirs interconnected to a horizontal pathway. Fig. 9b illustrates a schematic diagram of a network comprising rectilinear intersecting pathways. Fig. 9c illustrates a network comprising a radial arrangement of pathways. Fig. 9d illustrates a network including a plurality of vertical pathways intersecting a horizontal pathway. Fig. 30 9e illustrates a plurality of horizontal pathways connected by an intersecting sinuous pathway. It will be appreciated that networks can be arranged in alternative patterns or

any combination of patterns for defining a desired flow of liquid in device 10 in accordance with the teachings of the present invention.

Liquid samples can be introduced onto device 10 by using a variety of contact or non-contact dispensing techniques. In addition, the liquid sample can be placed onto a 5 reservoir or injected directly onto a pathway. One non-contact dispensing method is ink-jetting. Contact dispensing methods include pin tool spotting, pressurized capillary tubes or syringe tips. Fig. 10a illustrates a sample deposition tool 60 delivering material onto a circular reservoir pad 61. Figures 10b-e represent liquid deposition directly onto respective pathways 62b-e. The pathways can have square, round or tapered edge 10 termination.

Figs. 11a-11b illustrate an exemplary use of device 100 in accordance with the teachings of the present invention for detecting airborne chemicals in gaseous, particulate or aerosol form by absorption onto a liquid surface. Device 100 comprises network 102 which comprises rectilinear pathways 104a-104c between respective source reservoirs 15 105a-105c and target reservoirs 106a-106c.

Input 107 dispenses one or more reagents to one or more source reservoirs 105-105c. For example, input 107 can be a microsyringe. Network 102 resides on surface 108. Liquids received on network 102 can absorb airborne chemical species 109 while flowing on pathways 104a-104c. The liquid flow is enforced via differential heating 20 from source reservoir 105 to target reservoir 106. This differential heating is accomplished through heat source 111, which is coupled to bottom surface 112 at edge 114, and heat sink 113 located at edge 116 of device 100. Heat sink 113 can be formed by flowing coolant substance 117 through interior 115 of metal tube 118. If substrate 122 is formed of silicon or a metal, a linear temperature profile can be made to develop 25 along pathways 104a-104c. Other temperature profiles are possible in accordance with the teachings of the present invention.

Heat source 111 is placed in registry with source reservoirs 105a-105c. Heat source 111 can be a single activated heat source such as a flexible metal heater insulated with Kapton foil (e.g. Omega Engineering Inc. model KHLV-0502/10-P). Heat source 30 111 can be attached to bottom surface 112 of substrate 122 by means of glue or adhesive material. Alternatively, for transport along more curvilinear pathways 104, the

differential heating can be accomplished through a plurality of cells 20 or heater elements 16 which are located beneath pathways 104 and individually electronically activated.

Device 100 and device 10 can be utilized with a number of detection schemes.

One such method can include deposition of various inhibited fluorescent liquid 5 compounds onto reservoirs 105a-c which when contacted by an airborne agent either emit light directly or can be made fluorescent by further optical excitation. The fluorescence can be detected by optical sensors 120. A suitable optical detector assembly 120 comprise a laser diode, optical filters and a light detector probing target reservoirs 106a-106c. Alternatively, optical sensors can be positioned along one or more of pathways 10 104a-104c. Other detection methods can include monitoring color changes (with or without fluorescence), electrical conductivity, refractive index, light absorption, or temperature. Electrochemical detectors can also be used. It will be appreciated that alternative methods for detecting airborne species could be used in accordance with the 15 teachings of the present invention. The species can be introduced onto device 100 by passive absorption or by convective gas streams running perpendicular to pathways 104a-c.

Fig. 12 is a flow diagram of an exemplary process for fabrication of device 10 and corresponding results of each of the steps. In this description of the fabrication process flat topologies are used. The initial cleaning of substrate 12 is shown in block 70. The 20 particular cleaning procedure is dependent on the substrate material. For instance, glass can be cleaned by ultrasonic agitation in organic solvents and immersion in sulphuric acid and hydrogen peroxide. Block 71 represents the optional deposition of a passivation or adhesion layer 9. This can be accomplished, for example, by spin coating a thin layer of spin-on glass or chemical vapor deposition of silicon nitride. This layer serves to 25 promote adhesion of insulation layer 14 to substrate 12 or to create a reproducible and well characterized (i.e. passivated) surface on top of which subsequent layers can be deposited. Block 72 represents an optional thermal and insulation layer which, for example, can be accomplished by spin coating a thin layer of polyimide which is then baked for imidization. This layer reduces the power input required to maintain a desired 30 temperature distribution and prevents electrical contact between heating elements 16 and substrate 12. Block 73 depicts the deposition of heating elements 16. Heating elements

16 can be micropatterned including current leads for power input. Heating elements 16 can be formed of a conductive metal such as titanium, platinum, gold or chromium, or a non-metallic conductor such as silicon or indium tin oxide. Heating elements 16 can be deposited by photolithographic patterning of a photoresist layer and subsequent pattern transfer into the resistive heating material. Alternatively, heating elements 16 can be deposited by thermal evaporation of the metallic or non-metallic conductor or by other deposition methods.

In block 74, electrical insulator layer 17 is deposited over heating elements 16 and insulating layer 14 or substrate 12. For example, electrical insulator layer 17 can be deposited as a layer of silicon oxide. An additional planarization and/or passivation layer 8 can be introduced to provide a smooth, flat and reproducible surface for subsequent hydrophilic/hydrophobic surface patterning. Electrical insulator layers 17 and/or passivation layer 8 provide additional protection of device 10 from moisture invasion. An exemplary method for performing planarization is by depositing a material such as a polymeric material or spin on glass onto heating elements 16 and insulator layer 14 or substrate 12. An implementation of a passivation layer includes plasma enhanced deposition of a silicon nitride passivation layer. In an alternate method, the fabrication method starts with substrate 12 including cells comprising transistors 21 and leads for a matrix addressing scheme of cells 20. Before deposition of heating elements 16, contacts through insulator layer 14 and electrical insulation layer 17 are formed. Alternatively, heating elements 16 can be formed below insulator layer 14.

Block 75 depicts a chemical patterning step of surface 18. In one embodiment surface 18 is first prepared to be completely hydrophobic. Thereafter, surface 18 is then selectively patterned to reveal hydrophilic regions such as reservoirs 105 and 106 or pathways 104. The chemical patterning step, however, need not be subtractive, as described below. An additive method in which the hydrophilic layer 18 is selectively stamped with hydrophobic material to produce a surface of mixed wettability. Surfaces of mixed wettability comprising hydrophilic and hydrophobic regions are used to confine and direct liquids on substrates such as glass, silicon, Kapton and other polymeric materials. In one embodiment, hydrophilic or hydrophobic surface patterns are used to form networks in device 10. Hydrophilic and hydrophobic surface patterns can be

fabricated to be refreshable for re-establishing the coating after it has been removed, such as by mechanical abrasion or chemical attack induced by repeated use.

Conventional methods for creating hydrophobic surfaces include silanization or thiolization. Treatment with organic solutions containing octadecyltrichlorosilane or 5 perfluorinated compounds, such as fluorinated trichlorosilane, produce strongly hydrophobic surfaces on which water droplets assume contact angles in excess of about 90 degrees. Figure 13 illustrates a hydrophobizing scheme which uses alkylthiol compounds on gold. An attractive feature of this method is that undesired abrasion or chemical attack resulting from repeated use of the device can be healed by simply 10 refreshing the hydrophobic portions of surface 18 comprising the gold coated regions. Only these regions attract and bind the thiolized solution. Patterning of the hydrophobic layer can be performed by photolithography, reactive ion etching in an oxygen plasma or exposure to ultraviolet light.

The flow diagram shown in Figure 13 can in practice also be used independently 15 of device 10 for uses requiring liquid sample confinement on a substrate containing no heating elements. It can also be used on surfaces which are uniformly heated or cooled as in a microreactor plate. The flow diagram illustrates the method for fabricating refreshable hydrophilic and hydrophobic surface patterns. These process steps can also be performed on top of layer 17 following the process step shown in block 74.

20 In block 200, surfaces of the material on substrate 12 are cleaned. In an embodiment of the device, substrate 12 is a silicon wafer or glass plate. The material on substrate 12 can be immersed in sulfuric acid, hydrogen peroxide and deionized water at elevated temperatures. Cleaning of polymeric materials requires reagents compatible with the chemical resistance of the material on substrate 12. In block 201, a layer of Cr is 25 evaporated. The layer of Cr can have a thickness between about 1 and about 10 nanometers. In block 202, a layer of Au is evaporated. This layer of Au can have a thickness between about 1 to about 500 nm. In block 203, photoresist is spin coated onto the Au coated surface. In block 204, the photoresist is patterned by application of a mask and photolithographic processing for developing the exposed photoresist. In block 205, a 30 pattern is etched into the Au layer. A suitable etching technique can be wet chemical etching (TFA from Transene Comp. Inc). In block 206, any remaining photoresist is

removed. In block 207, the Au surface is coated with a hydrophobic material. Suitable hydrophobic substances include alkylthiols like hexadecanethiol. A monolayer of this material can be applied by immersion of the Au surface into a solution of alkylthiol in ethanol. The thiol molecules are known to bond selectively to Au surfaces. The thiol 5 molecules will not bond to substrates such as glass, silicon or Kapton. In block 208, if any of the hydrophobic material is removed by mechanical abrasion or chemical attack, the gold surface can then be reimmersed into the hydrophobic solution for material selective refreshing of the hydrophobic coating.

In an alternate method of fabricating refreshable surface patterns, blocks 201-205 10 can be substituted with a lift off process in which a layer of photoresist is patterned before the metal coating is evaporated. Alternatively, titanium can be used in step 201 and evaporated by the use of an electron beam evaporator.

The hydrophilicity of a chemically patterned substrate can be maintained by 15 storing it in glycerol ($C_3H_5(OH)_3$, 1,2,3-propanetriol). The glycerol can be applied by brushing, dipcoating or other coating technique. Once coated with a layer of glycerol, device 10 can be stored without degradation or organic contamination of the hydrophilic regions for extended periods of time. Upon use, the glycerol coating can be removed by washing the surface with deionized water and drying by a filtered gas stream like dry 20 nitrogen. Glycerol does not adhere to hydrophobic coatings and does not readily evaporate at room temperature. If the glycerol coated substrates are placed in a refrigerated environment, the glycerol will thicken to produce a gel-like protective coating. Since glycerol is hygroscopic, storage in an airtight container is preferable.

It is to be understood that the above-described embodiments are illustrative of 25 only a few of the many possible specific embodiments which can represent applications of the principles of the invention. Numerous and varied other arrangements can be readily devised in accordance with these principles by those skilled in the art without departing from the spirit and scope of the invention.

The thermal fluidic device described above can be used for applications involving 30 functional genomics and recombinant DNA methods. It can also be used for microarray immunoassays in microfluidic triage protein chips.

The invention described is also broadly applicable as a diagnostic and/or synthetic tool. Unlike other microfluidic technologies, its design enables manipulation, transport, and analysis of both droplets and continuous streams. It also uses only one single mechanism (i.e. an addressable thermal matrix array) to enforce precise dosing, transport, 5 mixing and chemical reactions. Allowing multiple and parallel reactions, the chip is ideally suited to the synthesis and screening of specialized inorganic, organic or genomic materials in the nano- to picoliter range by spatial and temporal multi-step manipulation of droplets. The manipulation and control of liquid samples can be used for fundamental studies, like the interrogation and modification of rate constants, molecular activity and 10 macromolecular conformation and phase changes in ultraconfined geometries in a completely automated manner producing quantities in the nano- to picoliter range. The device can also be used as a micro or nano-synthesis plate in which multiple organic or inorganic materials can be combined to form novel materials.

15 The invention described can also be used in combination with more traditional lab-on-a-chip devices which typically use pneumatic or electrokinetic mechanisms for flowing, sorting, sizing and quantitating biological material like nucleic acids. It also lends itself to high throughput applications.

20

EXAMPLE

Example I:

Prototypes for the sensor device depicted in Fig. 11a and 11b have been fabricated using the following process steps:

25

1. Cutting of silicon wafers into 2-by-2 inch pieces.
2. Cleaning of silicon samples by rinsing with or ultrasonication in tetrachlorethylene, acetone and isopropanol.
3. Further cleaning of silicon samples by immersion into a mixture of sulfuric acid, 30 hydrogen peroxide and deionized water at a temperature of 80°C for 20 minutes.
4. Deposition of a 120 nm thick layer of silicon dioxide by plasma enhanced chemical vapor deposition using a Plasmatherm 790 at a temperature of 250°C.
5. Deposition of a 120 nm thick layer of silicon nitride by plasma enhanced chemical vapor deposition using a Plasmatherm 790 at a temperature of 250°C.
- 35 6. Deposition of a 120 nm thick layer of silicon dioxide by plasma enhanced chemical vapor deposition using a Plasmatherm 790 at a temperature of 250°C.

7. Spin coating of a layer of photoresist (AZ5214 at 4000 rpm for 40 seconds), exposure to UV radiation in a Karl Suess MJB3 mask aligner with a photolithographic mask for the heating electrodes and development of photoresist using a Clariant 400k developer.
- 5 8. Evaporation of 5 nm thick layer of titanium, a 120 nm thick layer of Au and a 5 nm thick layer of Cr using a Denton electron beam evaporator.
9. Removal of resist by immersion into acetone, which leaves the desired metal heater and contact pads on the surface.
10. Deposition of a 600 – 800 nm thick silicon dioxide layer by plasma enhanced chemical vapor deposition using a Plasmatherm 790 at a temperature of 250°C with electrical contacts masked.
11. Spin-coating of a layer of photoresist (AZ5214 at 4000 rpm for 40 seconds), exposure to UV radiation in a Karl Suess MJB3 mask aligner with a photolithographic mask for straight parallel hydrophilic channels and development of the photoresist using Clariant 400k developer.
- 15 12. Immersion of sample in a dilute (1 mM) solution of 1H,1H,2H,2H- perfluoroctyltrichlorosilane in dodecane for 5 min.
13. Removal of sample from solution and sonication of sample in dodecane for 1-5 minutes.
- 20 14. Sample dried in stream of filtered nitrogen gas followed by a water rinse.
15. Rinsing of sample with acetone to remove photoresist.
16. Immersion of sample in Bakerstrip 1000 at a temperature of 60°C for 5 minutes.
17. Rinsing of sample with acetone and isopropanol.
- 25 18. Removal of silicon dioxide and chromium on top of contact pads using chromium etchant CR-7
19. Soldering of contact pads with In-solder.
20. Cleaning of hydrophilic regions with a dilute solution of sulfuric acid and hydrogen peroxide in deionized water.
21. Powering heating resistor with DC-power supply.
- 30 22. Placing edge of sample opposite to heater wire on water cooled brass block.
23. Deposition of hydrophilic liquid on the hydrophilic regions produces controllable and predictable liquid flow.

35 Example II:

Another prototype for the sensor device depicted in Fig. 1b and 1c has been fabricated using the following process steps:

- 40 1. Cutting of silicon wafers in 2-by-2 inch pieces
2. Cleaning of silicon samples by rinsing with or ultrasonication in tetrachlorethylene, acetone and isopropanol
3. Further cleaning of silicon samples by immersion into a mixture of sulfuric acid, hydrogen peroxide and deionized water at a temperature of 80°C for 20 minutes.
- 45 4. Spin-coating of a layer of photoresist (AZ5214 at 4000 rpm for 40 seconds), exposure to UV radiation in a Karl Suess MJB3 mask aligner with a

photolithographic mask for straight parallel hydrophilic channels and development of the photoresist using Clariant 400k developer

5. Immersion of sample in a dilute (1 mM) solution of 1H,1H,2H,2H-perfluoroctyltrichlorosilane in dodecane for 5 min.

5. 6. Removal of sample from solution and sonication of sample in dodecane for 1-5 minutes.

7. Sample dried in filtered nitrogen gas stream followed by a water rinse.

8. Rinsing of sample with acetone to remove photoresist.

9. Immersion of sample in Bakerstrip 1000 at a temperature of 60°C for 5 minutes

10. 10. Rinsing of sample with acetone and isopropanol

11. Removal of silicon dioxide and Cr on top of contact pads using chromium etchant CR-7

12. Soldering of contact pads with In-solder

13. Cleaning of hydrophilic regions with a dilute solution of sulfuric acid and hydrogen peroxide in deionized water

14. Place one edge of sample on heated, temperature controlled brass block.

15. Place opposite edge of sample on water cooled brass block.

16. Deposition of hydrophilic liquid on the hydrophilic regions produces controllable and predictable liquid flow. Proof of concept of this device was accomplished with a surface network consisting of a parallel set of rectilinear hydrophilic stripes each connecting two diamond shaped reservoirs. Only one resistive heater was patterned on the underside of a silicon substrate. The resistive heater assumed the shape of a long narrow stripe which ran perpendicular to the flow direction. The heater stripe warmed the surface at the point where the liquid exits the reservoir and enters the hydrophilic stripe.

20. Various hydrophilic liquid samples (e.g. polydimethylsiloxane, glycerol, or tetraethylene glycol) were each deposited onto a different reservoir pad and the liquids spread in a predictable and controllable fashion. The liquid speed was found to be well correlated to the power applied to the resistor (which determines the temperature difference between the heated and the cooled sample edge), the width of the hydrophilic stripe and the volume of liquid deposited. Higher power inputs, wider hydrophilic stripes, thicker rivulets and larger sample volumes produced faster flow rates. Liquids with lower viscosity or stronger variation of surface tension, γ with temperature T (i.e. higher $d\gamma/dT$) produced correspondingly faster speeds.

35. Example III:

A prototypes for the microfluidic routing device depicted in Fig. 1a has been fabricated using the following process steps:

40. 1. Cleaning of a 2-by-2 inch piece of Corning 1737 glass with a thickness of 0.7 mm by rinsing with (or ultrasonication in) tetrachlorethylene, acetone and isopropanol.

2. Further cleaning by immersion into a mixture of sulfuric acid, hydrogen peroxide and deionized water at a temperature of 80°C for 20 minutes.

3. Spin coating of a layer of photoresist (AZ5214 at 4000 rpm for 40 seconds), exposure to UV radiation in a Karl Suess MJB3 mask aligner with a

photolithographic mask for the heating electrodes and development of photoresist using Clariant 400k developer.

4. Evaporation of 120 nm thick layer of Ti, a 100 nm thick layer of Au and a 5 nm thick layer of Cr using a Denton electron beam evaporator.
5. Removal of resist by immersion into acetone, which leaves the desired metal heater and contact pads on the surface.
6. Deposition of a 600 – 800 nm thick silicon dioxide layer by plasma enhanced chemical vapor deposition using a Plasmatherm 790 at a temperature of 250°C with electrical contacts masked.
10. 7. Spin-coating of a layer of photoresist (AZ5214 at 4000 rpm for 40 seconds), exposure to UV radiation in a Karl Suess MJB3 mask aligner with a photolithographic mask for straight parallel hydrophilic channels and development of the photoresist using Clariant 400k developer.
8. Immersion of sample in a dilute (1 mM) solution of 1H,1H,2H,2H-15 perfluoroctyltrichlorosilane in dodecane for 5 min.
15. 9. Removal of sample from solution and sonication of sample in dodecane for 1-5 minutes.
10. 10. Drying of sample in filtered nitrogen stream following by a water rinse.
11. 11. Rinsing of sample with acetone to remove photoresist.
20. 12. Immersion of sample in Bakerstrip 1000 at a temperature of 60°C for 5 minutes.
13. Rinsing of sample with acetone and isopropanol.
14. Removal of silicon dioxide and Cr on top of contact pads using chromium etchant CR-7.
25. 15. Optional soldering of contact pads with In-solder.
16. Cleaning of hydrophilic regions with a dilute solution of sulfuric acid and hydrogen peroxide in deionized water.
17. Powering heater resistor with DC-power supply and alligator clips attached to the device.
30. 18. Sample placed on water cooled brass block which acts as heat sink.

It is to be understood that the above-described embodiments are illustrative of only a few of the many possible specific embodiments which can represent application of the principles of the invention. Numerous and varied other arrangements can be readily devised in accordance with these principles by those skilled in the art without departing from the spirit and scope of the invention.